REMARKS

Claims 1 and 3-18 are pending. Claims 5, 6, 11 and 14-16 are withdrawn. Claims 1, 3, 4, 7-10, 17 and 18 are under examination. In an Office Action mailed October 17, 2007, the Examiner withdrew rejections under 35 U.S.C. § 112, 1st and 2nd Paragraphs. The Examiner maintained a single rejection of the examined claims under 35 U.S.C. § 103(a) for alleged obviousness over Benvenisty et al. (US 2002/0127715 or WO 02/061033) in view of West et al. (U.S. 2004/0219563).

A Request for Continued Examination accompanies this response so that the finality of the rejection will be withdrawn and the response will be considered.

The Examiner alleged that the cited Benvenisty et al. application (Serial No. 09/995,452; Publication No. US 2002/0127715) teaches electroporation of genetic constructs into human embryonic stem cells. Applicants respectfully traverse the rejection. There is no more relevant evidence that the cited application is non-enabling than the words of the inventor of that application. Professor Nissam Benvenisty acknowledged under oath that Benvenisty et al. does not enable a person of ordinary skill to achieve electroporation of human embryonic stem cells to an extent that yields cells suited for performing other manipulations. Moreover, Dr. Benvenisty further declared that the present inventors, Drs. Zwaka and Thomson, were the first to publish a suitable electroporation method.

Applicants attach a complete copy of a Declaration filed October 27, 2004 (with Exhibits) in the prosecution history of the '452 application for the Examiner's consideration and review. Exhibit C to the Benvenisty Declaration is a report of the work by Drs. Zwaka and Thomson disclosed in Applicants' pending application and subsequently published. In the Declaration, Dr. Benvenisty declared, *inter alia,* that:

> 9. Although the Examiner points out that our application states that "human ES cells can be transfected by electroporation..." these were our own observations, not those reported by others working in the field. However, it should be emphasized that the yield obtained then (at the time of the present invention) when transfecting hES cells through electroporation was not feasible for performing further manipulations with the transfected cells and thus, we

abandoned this technology and searched for a substitute. Except for other publications from my laboratory, no other researcher reported successful transfection of human ES cells under the same conditions described in the present application, until the Zwaka et al. reference in 2003, a full three years after the priority date of this application, in spite of the wealth of information available concerning how to achieve successful transfection of ES cells in other animals, or how to achieve transfection of other cell types in both humans and other animals.

10. In addition, Zwaka et al. reported in their article that when a typical mouse ES cell electroporation protocol was tried as a means for introducing DNA into human ES cells, the results were so poor, and the rate of instruction so low ($\sim 10^{-7}$), that is was not practical to use mouse electroporation protocols for introduction DNA into human cells (*id.*). And significantly, Zwaka et al. also state that their "... failure to achieve homologous recombination with chemical transfection reagents led [them] to re-evaluate electroporation procedures for hum ES cells" (*see id.*, p. 319, first full para.), but this is a 2003 reference, indicating that until then, transfection of human ES cells using electroporation was not a viable means for introducing DNA into hES cells, and thus Smith *et al.* cannot be cited as prior art for an obviousness rejection.

11. Eiges et al., and Zwaka et al. provide substantial evidence that mouse protocols for introducing DNA into human ES cells did not work at the time this invention was submitted, even as last as 2003.The Zwaka and Eiges publications directly contradict Smith et al.'s claim, in the absence of *any* experimental evidence with human ES cells using electroporation or other means, that essentially *any* means will work for introducing a marker into *any* animal ES cells, including "transfection, lipofection, injection, ballistic missile, viral vector, or [...] electroporation" (see Smith et al., Col. 3, lines 63-64).

Benvenisty further declared, in paragraph 14, that "[a]s discussed earlier, electroporation may be a successful transfection technique for murine ES cells, but not for human ES cells. Also, homologous recombination techniques as taught by Bradley et al. may have some success with murine ES cells, but as Zwaka et al. showed, such homologous recombination techniques as applied to human ES cells are unsuccessful.

Benvenisty still further declared, in paragraph 16, that "the fact that we had to look for alternatives to electroporation, in 2001, and that Zwaka et al. reiterated that electroporation protocol as performed by mouse ES cells did not work for introducing DNA into hES cells, is

more evidence that the transferring of technology from one species to the other was not trivial." Benvenisty also declares that "as stated above, even electroporation techniques were not reported as a means for introducing DNA into *human* ES cells until the techniques reported by Zwaka et al. in 2003, in spite of the unsubstantiated assertions in Smith to the contrary."

Finally, Benvenisty declared, in paragraph 19, that "[a]s indicated above in Zwaka et al., the levels of successful introduction of DNA into hES cells using electroporation, even in 2003, were only ~10^{-7} and thus too low to be practical." (Zwaka et al., p. 319, col. 2, 1st para.).

Writing several years after his own filing date, Benvenisty acknowledged that a person having ordinary level of skill in the art would not have looked to his patent application for an enabling disclosure of electroporation of human ES cells and, further, that Zwaka et al. were the first to report successful electroporation of human ES cells (in the work disclosed in the pending application).

In view of this admission by Benvenisty, the Examiner's reliance upon the citation cannot be sustained. As West et al. provides no other independent teaching of electroporation into human ES cells, the rejections themselves cannot stand. Accordingly, reconsideration of the rejections under §103 is respectfully requested. Having addressed each outstanding ground of rejection, Applicants respectfully suggest that the claims are in condition for allowance.

Applicants also submit several additional documents including a subsequently published book chapter by the inventors and a paper that describes the inventors' work. Both are consistent with the information in the Benvenisty Declaration.

FEES

A petition for an extension of time for three months accompanies this response so the response will be deemed to have been timely filed. No other extension of time is believed due, but should any other extension of time be due in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the extension fee to Deposit Account 17-0055. No other fee is believed due, but should any fee be due in this or any

subsequent response, please consider this to be a request to charge the fee to the same Deposit Account.

Respectfully submitted,

/Bennett J. Berson/
Bennett J. Berson
Reg. No.: 37,094
Attorney for Applicants

TEL 608/251-5000
FAX 608/251-9166
QUARLES & BRADY LLP
P.O. Box 2113
Madison, WI 53701